Exhibit D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Examining Operations

Applicant(s): Hayden et al

Serial No: 09/526,193 Art Unit: 1652

Filed: 15 March 2000 Examiner: Steadman, D.

TITLE: METHODS AND REAGENTS FOR MODULATING CHOLESTEROL LEVELS

Docket No.: 760050-19

VIA EXPRESS MAIL

BOX AF
Commissioner for Patents
Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R. 1.116

Sir:

Regarding the Office Action dated 2 December 2002, Applicant requests that the Application be amended as follows:

In the Claims:

Please cancel claim 187 without prejudice.

Please amend the claims as follows:

135. (Three Times Amended) A process for identifying a compound that modulates ~~mammalian~~ human ABC1 (ABC1) polypeptide biological activity comprising contacting a compound with a human ABC1 polypeptide that has ABC1 biological activity and in the presence of adenosine triphosphate (ATP) under conditions

promoting the biological activity of said ABC1 polypeptide and detecting a difference in said biological activity following said contacting relative to when said compound is not present

wherein said biological activity is binding or hydrolysis of adenosine triphosphate (ATP) and wherein said human ABC1 (hABC1) comprises amino acids 1-60 of SEQ ID NO: 1,

thereby identifying an ABC1 modulating agent.

143. (Four Times Amended) A process for identifying a compound that modulates mammalian ABC1 polypeptide biological activity comprising contacting a compound with a membrane comprising a mammalian ABC1 polypeptide comprising an amino acid sequence with at least 85% identity to the amino acid sequence of SEQ ID NO: 1 and having lipid transporting activity, in the presence of a lipid under conditions promoting transport of said lipid across said membrane, wherein said lipid is phospholipid or cholesterol, and detecting a difference in said transport following said contacting relative to when said compound is not present thereby identifying a mammalian ABC1 modulating agent.

161. (Three Times Amended) A process for identifying a compound that modulates ~~mammalian~~ human ABC1 polypeptide biological activity and is useful in modulating plasma cholesterol levels in a mammal comprising contacting a compound with a membrane comprising a human ABC1 polypeptide, wherein said polypeptide comprises amino acid residues 1-60 of SEQ ID NO: 1, and a source of one or more anions under conditions promoting transport of said one or more anions across said membrane and detecting a difference in said transport following said contacting relative to when said compound is not present thereby identifying a mammalian ABC1 modulating agent.

166. (Three Times Amended) A process for identifying a compound that modulates ~~mammalian~~ human ABC1 polypeptide biological activity for use in treating

CAD comprising contacting a compound with a membrane comprising a human ABC1 polypeptide and interleukin-1 under conditions promoting transport of said interleukin-1 across said membrane and detecting a difference in said transport following said contacting relative to when said compound is not present and wherein said human ABC1 comprises amino acids 1-60 of SEQ ID NO: 1, thereby identifying a mammalian ABC1 modulating agent useful for treating CAD.

168. (Twice Amended) The process of claim ~~167~~ 166 wherein said human ABC1 comprises the amino acid sequence of SEQ ID NO: 1.

169. (Twice Amended) A process for identifying a compound that modulates ~~mammalian~~ human ABC1 protein biological activity and is useful in modulating human plasma cholesterol levels comprising contacting a compound with a human ABC1 protein that has ABC1 biological activity and in the presence of a protein that binds to said human ABC1 protein under conditions promoting binding of said protein to said ABC1 polypeptide, wherein said human ABC1 protein comprises amino acids 1-60 of SEQ ID NO: 1, and detecting a difference in said binding following said contacting relative to when said compound is not present thereby identifying a mammalian ABC1 modulating agent.

172. (Twice Amended) The process of claim 169 wherein said ABC1 polypeptide is present in the membrane ~~is part~~ of an intact cell.

176. (Twice Amended) A process for identifying a compound that modulates mutant human ABC1 (hABC1) polypeptide biological activity comprising contacting a compound with a mutant hABC1 polypeptide having ABC1 polypeptide biological activity, comprising from 1 to 5 amino acid differences relative to the sequence of SEQ ID NO: 1, and a member selected from the group consisting of a lipid, a protein, ATP, and interleukin-1, and detecting a difference in said biological activity following said

contacting relative to when said compound is not present thereby identifying a mutant hABC1 modulating agent.

179. (Twice Amended) The process of claim ~~143~~ 178 wherein said hABC1 comprises a detectable label.

181. (Twice Amended) The process of ~~claims~~ claim 143 wherein said ABC1 polypeptide is a recombinant polypeptide.

184. (Twice Amended) A process for identifying a compound that modulates cholesterol levels in a mammal comprising administering to said mammal an effective amount of a compound that has ABC1 modulating activity in the process of claim 143 and determining a difference in cholesterol level in said mammal following said administering thereby identifying a compound that modulates cholesterol levels in a mammal.

188. (Twice Amended) The process of claim ~~182~~ 184 wherein said mammal is a human.

213. (Twice Amended) A process for identifying a compound that modulates lipid transport across a mammalian cell that includes a cell membrane that includes ABC1 polypeptide comprising an amino acid sequence with least 85% identity to the amino acid sequence of SEQ ID NO: 1 and having lipid transporting activity, comprising testing ~~a~~ said mammalian cell ~~that~~ wherein said cell includes ~~in the cell~~ a lipid selected from the group consisting ~~of~~ of phospholipid and cholesterol, under conditions promoting transport of said lipid across said membrane, and comparing transport of said lipid in the presence and absence of a test compound whereby a difference in said transport indicates modulation, thereby identifying said compound as a modulator of lipid transport.

Please add the following new claims:

226. (New) The process of claim 143 wherein said percent identity is at least 90% identity.

227. (New) The process of claim 143 wherein said percent identity is at least 95% identity.

228. (New) The process of claim 143 wherein said ABC1 polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

229. (New) The process of claim 213 wherein said percent identity is at least 90% identity.

230. (New) The process of claim 213 wherein said percent identity is at least 95% identity.

231. (New) The process of claim 213 wherein said ABC1 polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

REMARKS

Applicants respond as follows:

Application Status

In accordance with the Examiner's request, a new complete claim set (including the amendments herein and newly added claims) is included as an attachment hereto. All amended claims are presented at the beginning, with editing marks included.

Drawings

New drawings were submitted with the labeling requirements of the Draftperson's Review on 11 February 2003.

Claim Objections

Claim 181 was objected to for grammatical reasons. Applicants have amended claim 181 to recite "claim 143" in place of "claims 143."

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 135, 161, 166 and 169, along with claims dependent therefrom, were rejected as indefinite for use of the term "mammalian" in the preamble of these claims. In response, Applicants have amended these claims to recite "human" in the preambles.

Claim 172 was rejected for indefiniteness for use of the term "membrane" when such term is not recited in parent claim 169. In response, Applicants have amended claim 172 to recite that the ABC1 polypeptide of claim 169 is in the membrane of an intact cell.

Claim 176 was rejected for indefiniteness for use of the term "mutant hABC1 polypeptide" without mentioning whether the mutant polypeptide has biological activity

or the scope of the biological activities involved. In response, Claims 176 and 178 have been amended to recite that the mutant ABC1 has biological activity, as defined on page 15 lines 10-14.

Claim 184 was rejected as indefinite for use of the phrase "following said thereby." In response, Applicants have amended this claim to add the term "administering" after "following said."

Claim 168 was rejected as indefinite for dependence from cancelled claim 167. In response, Applicants have amended claim 188 to depend from claim 166.

Claim 188 was rejected as indefinite for dependence from cancelled claim 182. In response, Applicants have amended claim 188 to depend from claim 184.

Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 143-145, 148, 149, 151, 156-158, 176, 178-181, and 213-225 were rejected under section 112 as failing to meet the written description requirement.

The rejection continues to argue that, although the polypeptides are not being claimed, the specification fail to disclose a sufficient number of ABC1 polypeptides to show that Applicants were in possession of the invention. In response, Applicants have amended the generic claims to clarify the polypeptide involved.

Claim 143 (and claims dependent therefrom) has been amended to recite a biological membrane comprising an ABC1 polypeptide with at least 85% identity to the amino acid sequence of SEQ ID NO: 1 and having lipid transport activity. This amendment is supported by the disclosure of the application as filed, especially at page 15, lines 8-9, where an ABC1 polypeptide is defined as "a polypeptide having

substantial identity to an ABC1 polypeptide having the amino acid sequence of SEQ ID NO: 1" and at page 12, lines 9-11, where "substantially identical" is defined as having preferably at least 85% identity. Thus, in defining the percent identity with human ABC1 of SEQ ID NO: 1 and the activity being assayed, Applicants believe that the grounds of the rejection have been overcome.

Applicants have also added new claims 226-228 depending from claim 143 and limiting percent identity to, respectively, 90%, 95% and having the sequence of SEQ ID NO: 1.

Claim 213 (and claims dependent therefrom) has been amended to add the limitation of lipid transporting activity and at least 85% identity of the ABC1 to SEQ ID NO: 1. Some additional modifications were made to this claim for purposes of clarifying the recited process but do not change the claim elements.

Applicants have also added new claims 229-231 depending from claim 213 and limiting percent identity to, respectively, 90%, 95% and 100%.

Claims 176 and 178 were rejected on similar grounds. In response, Applicants have amended claim 176 (and thus claim 178 also) by adding the limitation that the mutant ABC1 has ABC1 biological activity, said activity being defined in the application at page 15, lines 10-14, as well as throughout the application.

The remaining rejected claims all depend, either directly or indirectly, from either claim 143 or claim 213, which have been amended.

In the interests of clarity and continuity, claim 179 was amended to depend from claim 178 in place of claim 143 because a labeled hABC1 protein is useful in protein stability assays, such as with mutant ABCs more than in lipid transport (where it is the

lipid that might be labeled). This should have depended on claim 178 is supported in the specification at page 62, line 26 over to page 63, line 7.

Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 143-145, 148, 149, 151, 156-158, 176, 178-181, and 213-225 were rejected under section 112 as failing to meet the written description requirement.

The argument of the rejection is similar to that for written description: insufficient numbers of mammalian polypeptides have been disclosed in the application.

In response, Applicants note that this is the same set of claims rejected under the written description rejection and Applicants' response is substantially the same as that above with the same amendments overcoming this ground of rejection also.

No fee is believed due in filing this response. If any fee is due, the Commissioner is requested to charge such fees, or credit any refunds, to Deposit Acc't No. 03-0678.

EXPRESS MAIL CERTIFICATE

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Deposit Date: 6 March 2003

I hereby certify that this paper and the attachments hereto are being deposited today with the U.S. Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above addressed to:

BOX AF
Commissioner for Patents
Washington, DC 20231

Alan J. Grant 3/6/03
Alan J. Grant, Esq. **Date**

Respectfully submitted,

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COMPLETE PENDING CLAIM SET

135. (Three Times Amended) A process for identifying a compound that modulates human ABC1 (ABC1) polypeptide biological activity comprising contacting a compound with a human ABC1 polypeptide that has ABC1 biological activity and in the presence of adenosine triphosphate (ATP) under conditions promoting the biological activity of said ABC1 polypeptide and detecting a difference in said biological activity following said contacting relative to when said compound is not present

wherein said biological activity is binding or hydrolysis of adenosine triphosphate (ATP) and wherein said human ABC1 (hABC1) comprises amino acids 1-60 of SEQ ID NO: 1,

thereby identifying an ABC1 modulating agent.

136. (Amended) The process of claim 135 wherein said difference in biological activity is an increase in biological activity.

142. (Amended) The process of claim 135 wherein said human ABC1 (hABC1) comprises the amino acid sequence of SEQ ID NO: 1.

143. (Three Times Amended) A process for identifying a compound that modulates mammalian ABC1 polypeptide biological activity comprising contacting a compound with a membrane comprising a mammalian ABC1 polypeptide having an amino acid sequence with at least 85% identity to the amino acid sequence of SEQ ID NO: 1 and having lipid transporting activity, in the presence of a lipid under conditions promoting transport of said lipid across said membrane, wherein said lipid is phospholipid or cholesterol, and detecting a difference in said transport following said contacting relative to when said compound is not present thereby identifying a mammalian ABC1 modulating agent.

144. (Amended) The process of claim 143 further comprising contact with an acceptor that accepts the transported lipid, said acceptor being a member selected from the group consisting of phospholipid, high density lipoprotein (HDL), Apolipoprotein (Apo) AI, ApoAII and ApoE.

145. (Amended) The process of claim 143 wherein said compound is useful in treating coronary artery disease (CAD).

147. The process of claim 144 wherein said acceptor is a phospholipid.

148. The process of claim 143 wherein said membrane is part of an intact cell.

149. (Amended) The process of claim 148 wherein said cell is a fibroblast or a macrophage.

150. The process of claim 148 wherein said cell is a macrophage.

151. The process of claim 148 wherein said cell is a recombinant cell.

156. The process of claim 143 wherein said transport is cholesterol efflux.

157. The process of claim 143 wherein said mammalian ABC1 is mouse ABC1.

158. (Amended) The process of claim 143 wherein said mammalian ABC1 is human ABC1.

159. (Amended) The process of claim 158 wherein said human ABC1 comprises amino acid residues 1-60 of SEQ ID NO: 1.

160. (Amended) The process of claim 158 wherein said human ABC1 comprises the amino acid sequence of SEQ ID NO: 1.

161. (Three Times Amended) A process for identifying a compound that modulates human ABC1 polypeptide biological activity and is useful in modulating plasma cholesterol levels in a mammal comprising contacting a compound with a membrane comprising a human ABC1 polypeptide, wherein said polypeptide comprises amino acid residues 1-60 of SEQ ID NO: 1, and a source of one or more anions under conditions promoting transport of said one or more anions across said membrane and detecting a difference in said transport following said contacting relative to when said compound is not present thereby identifying a mammalian ABC1 modulating agent.

162. (Amended) The process of claim 161 wherein said difference in anion transport is an increase in said transport.

163. (Amended) The process of claim 161 wherein when said one or more anions comprises at least two different anions.

165. (Twice Amended) The process of claim 161 wherein said human ABC1 comprises the amino acid sequence of SEQ ID NO: 1.

166. (Three Times Amended) A process for identifying a compound that modulates human ABC1 polypeptide biological activity for use in treating CAD comprising contacting a compound with a membrane comprising a human ABC1 polypeptide and interleukin-1 under conditions promoting transport of said interleukin-1 across said membrane and detecting a difference in said transport following said contacting relative to when said compound is not present and wherein said human ABC1 comprises amino acids 1-60 of SEQ ID NO: 1, thereby identifying a mammalian ABC1 modulating agent useful for treating CAD.

168. (Amended) The process of claim 166 wherein said human ABC1 comprises the amino acid sequence of SEQ ID NO: 1.

169. (Twice Amended) A process for identifying a compound that modulates human ABC1 protein biological activity and is useful in modulating human plasma cholesterol levels comprising contacting a compound with a human ABC1 protein that has ABC1 biological activity and in the presence of a protein that binds to said human ABC1 protein under conditions promoting binding of said protein to said ABC1 polypeptide, wherein said human ABC1 protein comprises amino acids 1-60 of SEQ ID NO: 1, and detecting a difference in said binding following said contacting relative to when said compound is not present thereby identifying a mammalian ABC1 modulating agent.

172. (Twice Amended) The process of claim 169 wherein said ABC1 polypeptide is present in the membrane of an intact cell.

173. (Amended) The process of claim 172 wherein said cell is a recombinant cell.

174. (Amended) The process of claim 161 wherein said membrane is part of an intact cell.

175. (Amended) The process of claim 166 wherein said membrane is part of an intact cell.

176. (Twice Amended) A process for identifying a compound that modulates mutant human ABC1 (hABC1) polypeptide biological activity comprising contacting a compound with a mutant hABC1 polypeptide having ABC1 polypeptide biological activity, comprising from 1 to 5 amino acid differences relative to the sequence of SEQ ID NO: 1, and a member selected from the group consisting of a lipid, a protein, ATP, and interleukin-1, and detecting a difference in said biological activity following said

contacting relative to when said compound is not present thereby identifying a mutant hABC1 modulating agent.

178. The process of claim 176 wherein said mutant hABC1 polypeptide comprises a single amino acid difference relative to the sequence of SEQ ID NO: 1.

179. (Twice Amended) The process of claim 178 wherein said hABC1 comprises a detectable label.

180. The process of claim 179 wherein said label is a fluorescent label.

181. (Twice Amended) The process of claim 143 wherein said ABC1 polypeptide is a recombinant polypeptide.

213. (Twice Amended) A process for identifying a compound that modulates lipid transport across a mammalian cell that includes a cell membrane that includes ABC1 polypeptide comprising an amino acid sequence with least 85% identity to the amino acid sequence of SEQ ID NO: 1 and having lipid transporting activity, comprising testing said mammalian cell wherein said cell includes a lipid selected from the group consisting of phospholipid and cholesterol, under conditions promoting transport of said lipid across said membrane, and comparing transport of said lipid in the presence and absence of a test compound whereby a difference in said transport indicates modulation, thereby identifying said compound as a modulator of lipid transport.

214. The process of claim 213 wherein said modulation is an increase in lipid transport.

215. The process of claim 213 wherein said modulation is a decrease in lipid transport.

216. The process of claim 213 wherein said mammalian cell is a fibroblast.

217. The process of claim 213 wherein said mammalian cell is a mouse cell.

218 The process of claim 213 wherein said mammalian cell is a human cell.

219. The process of claim 213 wherein said lipid is phospholipid.

220. The process of claim 213 wherein said lipid is cholesterol.

221. The process of claim 213 further comprising the presence of an acceptor that accepts the transported lipid, said acceptor being a member selected from the group consisting of phospholipid, high density lipoprotein (HDL), Apolipoprotein (Apo) AI, ApoAII and ApoE.

222. The process of claim 221 wherein said acceptor is HDL.

223. The process of claim 213 wherein said mammalian cell is a recombinant cell.

224. The process of claim 143 wherein said modulation is an increase in transport.

225. The process of claim 143 wherein said modulation is a decrease in transport.

226. The process of claim 143 wherein said percent identity is at least 90% identity.

227. The process of claim 143 wherein said percent identity is at least 95% identity.

228. The process of claim 143 wherein said ABC1 polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

229. The process of claim 213 wherein said percent identity is at least 90% identity.

230. The process of claim 213 wherein said percent identity is at least 95% identity.

231. The process of claim 213 wherein said ABC1 polypeptide comprises the amino acid sequence of SEQ ID NO: 1.